Letters

RESEARCH LETTER

Single- vs Multiple-Fraction Radiotherapy for Bone Metastases From Prostate Cancer

Palliative radiotherapy, comprising 1 or more fractions (ie, treatments) of daily radiation, is the mainstay of treatment for painful bone metastases. In 2005, a US-based randomized trial demonstrated no difference in pain relief between single- and multiple-fraction radiotherapy for uncomplicated bone metastases, confirming results from international trials.[1,2]

The Choosing Wisely campaign advocates single-fraction treatment for bone metastases.[3] We examined whether single-fraction treatment has been incorporated into routine clinical practice for Medicare beneficiaries with prostate cancer and at what cost savings.

Methods | The Surveillance, Epidemiology and End Results (SEER)-Medicare database links patient data collected by SEER cancer registries to longitudinal Medicare claims.[4] We selected patients aged 65 years or older with prostate cancer and identified bone metastases (*International Classification of Diseases, Ninth Revision,* diagnosis code 198.5) and subsequent courses of radiotherapy from January 1, 2006, through December 31, 2009.

For each patient, we identified the initial outpatient course of radiotherapy following the first diagnosis of bone metastasis (index course) and ascertained the dates and number of radiotherapy fractions based on Medicare claims for radiation delivery (Medicare reimburses each radiotherapy fraction individually). Gaps between fractions of 14 days or longer were presumed to indicate new courses of radiotherapy.

Total and radiotherapy-related health care expenditures were calculated from the amount reimbursed by Medicare from the inpatient, outpatient, and physician/supplier component files from 15 days before the initial radiotherapy treatment date to 30 days posttreatment and were adjusted for inflation to 2009. Radiotherapy-related expenditures were calculated by summing *Current Procedural Terminology* codes between 77261 and 77999.[5]

We classified patients into single- or multiple-fraction treatment groups. We compared prognosis between the groups by evaluating survival estimates (palliative radiotherapy is not associated with survival improvements). We compared mean expenditures using analysis of variance. In sensitivity analysis, we restricted the cohort to patients without prior complicating events, including radiation, bone surgery, cord compression, or pathologic fracture.

Analyses were conducted using Stata version 12.1 (StataCorp). Statistical significance was set at .05 and all tests were 2-sided. The study was approved with a waiver of informed consent by the University of Pennsylvania institutional review board.

Results | Of 3050 patients, the median age was 78 years (interquartile range, 73-83 years), 85% were white, and 82% had 2 or more comorbid illnesses. Of these patients, 3.3% (95% CI, 2.7%-3.9%) had single-fraction radiotherapy and 50.3% (95% CI, 48.5%-52.1%) received more than 10 fractions (**Table**). In a sensitivity analysis restricted to 2028 patients without prior complicating events, 3.8% (95% CI, 3.0%-4.6%) had single-fraction radiotherapy.

Unadjusted median survival following the index radiotherapy course was lower in the single- compared with the multiple-fraction treatment group (5.0 months [95% CI, 3.6-10.5 months] vs 11.9 months [95% CI, 11.2-12.7 months], respectively; log-rank $P < .001$). Among patients who survived more than 6 months, 51.7% (1076/2080) received subsequent radiation treatment (no significant difference between groups, $P = .47$).

Mean 45-day radiotherapy-related expenditures were 62% lower for patients treated with single relative to multiple fractions ($1873 for single vs $4967 for multiple fractions; difference, $3094 [95% CI, $2107 to $4081]; $P < .001$). Mean 45-day total health care expenditures were $13 112 for single and $11 702 for multiple fractions (difference, $1409 [95% CI, −$568 to $3386]; $P = .16$). Mean 45-day total expenditures were substantial for patients who received single-fraction treatment because they were closer to death and using other medical services.

Discussion | Despite evidence demonstrating comparable pain relief for single-fraction treatment, only 3.3% of Medicare beneficiaries with bone metastases from prostate cancer received single-fraction treatment. Patients who received single-

Table. Radiotherapy for Bone Metastases From Prostate Cancer, 2006 to 2009

No. of Radiotherapy Fractions	Medicare Beneficiaries, No. (%) [95% CI]	Expenditures, Mean (95% CI), $	
		Radiotherapy-Related	Total
1	101 (3.3) [2.7-3.9]	1873 (903-2843)	13 112 (11 168-15 055)
2-5	395 (13.0) [11.8-14.1]	4967 (4787-5147)[a]	11 702 (11 343-12 062)[a]
6-10	1020 (33.4) [31.8-35.1]		
11-20	1177 (38.6) [36.9-40.2]		
>20	357 (11.7) [10.6-12.8]		

[a] These values are the mean expenditures for 2 through 20 or more radiotherapy fractions.

fraction radiotherapy had poorer prognoses, perhaps reflecting the perception that single-fraction treatment should be reserved for patients with limited life expectancy or poor performance status.[6] However, single-fraction treatment has substantial benefits for patient-centric palliative care, including greater quality of life and convenience, reduced travel time, and lower treatment costs.

We were unable to differentiate complicated from uncomplicated bone metastases (though sensitivity analyses to address this limitation revealed similar results). In addition, Medicare claims data cannot differentiate retreatment from treatment of another anatomic site.

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Author Contributions: Dr Bekelman had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Bekelman, Epstein, Emanuel.
Acquisition of data: Bekelman.
Analysis and interpretation of data: Bekelman, Epstein.
Drafting of the manuscript: Bekelman, Emanuel.
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COMMENT & RESPONSE

Assays for Cardiac Troponins

To the Editor The review by Dr de Lemos[1] highlighted the central role of cardiac troponins in the diagnosis of acute coronary syndrome. The statement that myocardial infarction (MI) is a clinical diagnosis with cardiac troponins merely an indicator of myocardial necrosis cannot be overemphasized.

In general, the expectation exists that highly sensitive assays for cardiac troponins will improve diagnostic sensitivity and discrimination for MI and that these assays will be associated with an increased number of patients with elevated levels of cardiac troponins.[2] The highly sensitive nomenclature refers to the analytical sensitivity of an assay or the capability to reliably measure small amounts of an analyte.

In contrast, diagnostic sensitivity or the proportion of patients with the disease and a positive test largely depends on the cutoff value used and the accuracy of the clinical diagnosis. This is reflected in the diagnostic sensitivities of the 2 assays for cardiac troponin I referred to as identical despite their dissimilar analytical sensitivities.[2] In the study by Reichlin et al,[3] the highly sensitive assay for cardiac troponin T and the analytically less sensitive assay for cardiac troponin I had identical areas under the curve, and the differences in diagnostic sensitivity were solely a function of the selected cutoff values used. Similar findings were recently reported concerning different generations of assays for cardiac troponin T.[4] Understanding the difference between analytical and diagnostic sensitivity parameters of an assay is important.

As de Lemos pointed out, the universal definition of MI provides no guidance on defining the magnitude of change required, and highly sensitive assays for cardiac troponins may prove valuable because they may detect significant temporal changes earlier. No standardized approach exists and percentage change or delta cutoff values for troponins are determined empirically, complicated by inconsistent percentage change calculations. This is demonstrated by the broad range of contradictory cutoff values cited.[1]

We have advocated for a logical guideline to define a significant change in serial cardiac troponin concentrations based on reference change values.[5] By following sound